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RESEARCH ARTICLE

Clinical Applicability of Transient Elastography for Estimating Liver Stiffness in Patients with Type 2 Diabetes Mellitus

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Abstract:

Background:

Type 2 diabetes mellitus (T2DM) is a risk factor for the development of non-alcoholic fatty liver disease, which can lead to liver fibrosis and ultimately to cirrhosis. Transient elastography (TE), by using the FibroScan, and is a non-invasive ultrasonography method to measure liver elasticity. TE has been related with the degree of liver fibrosis.

Objective:

To investigate the applicability of TE in daily clinical practice among T2DM patients.

Method:

In a non-academic teaching hospital, T2DM patients without a history of liver disease the degree of liver stiffness was measured using TE. Successful measurements were defined as 10 validated measurements per patient and an interquartile range (IQR) to median ratio of $\leq 30\%$.

Results:

In 90 of 126 patients (71%) valid measurements were obtained. Among the patients with invalid measurements, 33 had < 10 valid measurements and 3 had a IQR to median ratio of $< 30\%$. The percentage of invalid measurements was 12% in patients with a BMI $< 30 \text{ kg/m}^2$ and 39% in patients with a BMI $\geq 30 \text{ kg/m}^2$. Among the 90 patients with valid liver stiffness measurements, the median liver stiffness was 6.7 [4.6-8.5] kPa with a IQR of measurements of 1.1 [0.6-1.8] kPa and IQR to median ratio of 17 (13-23)%.

Conclusion:

The success rate of TE measurements using the FibroScan in patients with T2DM was 71%, with a lower success rate in patients with a BMI $\geq 30 \text{ kg/m}^2$. This diagnostic modality needs further investigation being introduced as a marker of fibrosis in daily diabetes practice.

Keywords: FibroScan, Fibrosis, NAFLD, Transient elastography, Type 2 diabetes mellitus.

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INTRODUCTION

In the Western society, 20-30% of the people are considered to have Non-Alcoholic Fatty Liver Disease (NAFLD). The spectrum of NAFLD ranges from mild hepatic steatosis to Non-Alcoholic SteatoHepatitis (NASH) [1]. If left untreated, NASH can progress to fibrosis, cirrhosis and eventually to the development of hepatocellular carcinoma [2]. Central obesity, dyslipidaemia and hypertension are risk factors for the development of NAFLD [3]. Persons with type 2 diabetes mellitus (T2DM) have an increased risk of developing NAFLD and also for progressing to cirrhosis and hepatocellular carcinoma [4 - 10].

At present, a liver biopsy is the gold standard to diagnose and determine the severity of NAFLD [11]. Because a liver biopsy is an invasive and laborious procedure, with possibly even (severe) complications, there is a search for non-invasive methods for estimating the degree of fibrosis [12]. One of these new procedures is measurement of the degree of liver fibrosis through transient elastography (TE) by FibroScan[®], a non-invasive ultrasound examination measuring liver elasticity. At present, the Fibroscan is already used in the management of hepatitis B and C.

Given the possible consequences of liver fibrosis there is growing interest in non-invasive methods for estimating the risk of liver related complications such as TE. Therefore we aimed to investigate the applicability of TE in daily clinical use in a secondary setting.

MATERIALS AND METHODS

Study Design and Population

The present study was a pilot study, conducted among patients with T2DM treated at the diabetes outpatient clinic of the Isala (Zwolle, The Netherlands), a large non-academic teaching hospital. Consecutive patients were recruited from the diabetes outpatient clinic, from June 2013 to August 2013. All patients aged 18 years or older with T2DM and willing to participate were included. Participants with diabetes secondary to chronic pancreatitis, haemochromatosis, genetically induced liver disease, known substance abuse or chronic viral hepatitis were excluded. The study protocol (study registration number 13.0433 B 10111832) was approved by the local medical ethics committee and the study was performed in accordance with the Declaration of Helsinki.

Measurements and Study Procedures

Liver stiffness measurements were performed using TE (FibroScan[®] 402, EchoSens, Paris, France) by one trained investigator (SH), according to a standardized examination procedure which has been described in detail previously [13]. A successful examination was defined as 10 validated measurements and an interquartile range (IQR) to median ratio of $\leq 30\%$ [14]. The standard medium (M)-probe was used for all patients, with a frequency of 3.5 MHz and a measurement depth of 25 to 65 mm.

At the first visit, clinical and biological parameters were recorded according to standardized protocol; Body Mass Index (BMI in kg/m²), waist circumference (cm), blood pressure (mmHg), alcohol use (number of units per day) and tobacco use (pack years), medication use, duration of diabetes, microvascular (nephropathy, retinopathy or neuropathy) and macrovascular complications. Patients were considered to have macrovascular complications when they had a previous history of myocardial infarction, percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting (CABG), stroke (CVA) or peripheral arterial disease. Peripheral arterial disease was defined as an ankle brachial index < 0.9 . Most recent laboratory values were collected: platelet count, prothrombin time (PT), creatinine, alkaline phosphatase (ALP), γ -glutamyl-transpeptidase (γ GT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glycated haemoglobin (HbA1c) and urinary albumin/creatinine ratio. Laboratory data were determined using standard hospital procedures, performed at the department of clinical chemistry of the Isala Hospital. HbA1c was measured using affinity chromatography high-performance liquid chromatography [15].

Primary and Secondary Outcomes

The primary outcome was defined as the percentage of valid measurements of liver elasticity. Secondary outcome measures included the outcomes of the liver elastic measurements, clinical differences in patients with and without valid measurements and differences according to BMI.

Statistical Analysis

All data were expressed as number (%), mean \pm standard deviation or median [interquartile range], as appropriate. Normality was evaluated using Q-Q plots and histograms. For continuous data, comparisons between groups were assessed using the Wilcoxon rank sum test. Categorical variables were compared by χ^2 -test. Statistical analyses were performed using the statistical commercial software IBM SPSS Statistics Version 21.0. A two-sided p-value of <0.05 was considered to be statistically significant.

RESULTS

Patients

From June 3 through August 27, 2013, a total of 191 individuals with T2DM were assessed for eligibility and received information about the study. During the subsequent outpatient clinic visit, 56 patients declined to participate and 9 did not meet the inclusion criteria due to no diagnosis of T2DM ($n=5$) or a diagnosis of haemochromatosis ($n=4$). Subsequently, TE measurements were conducted in 126 patients. As presented in Table 1, the mean age of these patients was 65.2 ± 12.8 years, 51% was male and the median body mass index (BMI) was 31.4 [28.3 - 34.6] kg/m^2 .

Table 1. Baseline characteristics and comparisons between patients with and without valid measurements.

	All (N=126)	Invalid measurements (N=36)	Valid measurements (N=90)
Male sex	64 (50.8)	15 (41.7)	49 (54.4)
Age (years)	65.2 ± 12.8	67.2 ± 11.7	64.4 ± 13.2
BMI (kg/m^2)	31.4 [28.3 - 34.6]	33.1 [30.7 - 36.4]*	30.3 [27.3 - 33.3]*
Systolic blood pressure (mmHg)	130.5 ± 15.3	134.9 ± 15.5	133.0 ± 15.3
Alcohol use (units of alcohol/day)	0.0 [0.0-1.0]	0.0 [0.0-0.3]	0.0 [0.0-1.0]
Tobacco use (pack/year)	6.4 [0-24.7]	5.5 [0-33.9]	6.9 [0-22.9]
Duration of diabetes (years)	15.2 ± 8.8	16.0 ± 6.8	14.9 ± 9.5
Medication diabetes (%)	124 (98.4)	36 (100)	88 (97.8)
Oral (%)	84 (66.7)	24 (66.7)	60 (66.7)
Metformin (%)	70 (55.6)	16 (44.4)	54 (60.0)
Insulin (%)	104 (82.5)	33 (91.7)	71 (78.9)
Microvascular complications (%)	91 (72.2)	30 (83.3)	61 (67.8)
Macrovascular complications (%)	50 (39.7)	19 (52.8)	31 (34.4)
Myocardial infarction (%)	32 (25.4)	9 (25.0)	23 (25.6)
PTCA (%)	23 (18.3)	8 (22.2)	15 (16.7)
CABG (%)	20 (15.9)	4 (11.1)	16 (17.8)
Stroke (%)	12 (9.5)	6 (16.7)	6 (6.7)
Arterial disease (%)	11 (8.7)	3 (8.3)	8 (8.9)

Results are expressed as $n(\%)$, mean \pm SE or median [IQR]. * p-value <0.05 , comparison between groups. Abbreviations: BMI, Body Mass Index; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; IQR, interquartile range.

Primary Outcome

Amongst the 126 TE measurements performed, 36 persons (28.6%) had an invalid measurement, translating into a success rate of 71.4%. Among the patients with an invalid measurement, 33 had < 10 valid measurements and 3 had a IQR to median ratio of $< 30\%$.

Secondary Outcomes

Among the 90 patients with valid liver stiffness measurements, the median liver stiffness was 6.7 [4.6 - 8.5] kPa with a IQR of measurements of 1.1 [0.6 - 1.8] kPa and IQR to median ratio of 17 (13-23)%. Besides a higher BMI (33.1 [30.7 - 36.4] vs. 30.3 [27.3 - 33.3] kg/m^2 , $p=0.001$) there were no clinical differences between patients with and without valid measurements (see Table 1).

In patients with a BMI ≥ 30 kg/m^2 ($n=77$), significantly less valid liver stiffness measurements were obtained than in patients with a lower BMI (61% vs. 88%, $p=0.001$). In multivariate analysis the median liver stiffness among patients with a valid measurement was not associated with age, BMI, alcohol use and ASAT concentrations.

DISCUSSION

TE, using the FibroScan, is an interesting and emerging non-invasive ultrasonography method to measure liver elasticity [13]. TE has been related with the degree of liver fibrosis. The aim of our study was to investigate the applicability of TE in clinical practice among T2DM patients without a known history of liver disease. The success rate of TE measurements was 71%, with a lower success rate among obese patients ($\text{BMI} \geq 30 \text{ kg/m}^2$).

This success rate is somewhat lower than the success rate of 82% found in the only previous study by De Ledinghen *et al.* investigating diabetes patients treated in a tertiary care setting [16]. The higher average BMI, recently demonstrated to negatively influence the success rate of TE, in the present study ($31.8 \pm 5.3 \text{ kg/m}^2$ vs. $25.3 \pm 4.5 \text{ kg/m}^2$) could explain this difference [17]. Moreover, the use of the M-probe in the present study may also account for the lower success rate found in the present study. Since the M-probe reached depths of 25 to 65 mm, in quite a few subjects subcutaneous fat accumulation hampered the sound waves even reaching the liver or preventing sufficiently reliable and reproducible measurements. Although speculative, the use of a recently developed XL-probe, specifically designed for patients with a high BMI, would possibly have led to more valid measurements [18, 19].

Among patients with valid liver stiffness measurements, the median liver stiffness was 6.7 [4.6-8.5] kPa. For post-hoc hypothesis generation we used a cut-off point of 8.7 kPa, in accordance with Wong *et al.* who defined a best cut-off value for METAVIR fibrosis score F3 (numerous septa present but no cirrhosis) or greater, *i.e.* METAVIR fibrosis score F4 (cirrhosis present), of 8.7 kPa in TE measurements as abnormal [20]. Using this cut-off value, 22.2% of patients with a valid measurement had a TE measurement >8.7 kPa. As compared to patients with a measurement <8.7 kPa, these patients had a significantly higher BMI, used tobacco more frequently, had more macrovascular complications and had higher γGT concentrations (see **Appendix 1**). Furthermore, there appeared to be a relatively strong positive correlation ($r=0.84$, $N=39$, $p<0.001$) between liver stiffness and the concentration of γGT (U/L) (see **Appendix 1**). Nevertheless, it should be concluded that the clinical relevance of the present study is unclear at present and requires further investigation.

CONCLUSION

In the present study the success rate of TE measurements using the FibroScan in patients with T2DM was 71%, with a lower success rate in patients with a $\text{BMI} \geq 30 \text{ kg/m}^2$. Based on our data routinely performing TE as a screening instrument should not be recommended. Although promising, this diagnostic modality needs further investigation being introduced as a marker of fibrosis in daily diabetes practice.

APPENDIX

Appendix 1. Post-hoc analysis among persons with valid measurements, above and below 8.7kPa.

	TE result ≤ 8.7 kPa (N=70)	TE result > 8.7 kPa (N=20)
Male sex	39 (55.7)	10 (50.0)
Age (years)	65.0 ± 12.8	62.4 ± 14.5
BMI (kg/m ²)	$29.6 [26.9-32.4]$	$32.2 [29.2-35.1]$ *
Systolic blood pressure (mmHg)	133.9 ± 16.3	129.6 ± 10.5
Alcohol use (units of alcohol/day)	0.86	0.81
Tobacco use (pack/year)	4.3 (0-20.0)	19.3 (0.8-39.0) *
Duration of diabetes (years)	14.9 ± 9.6	14.7 ± 9.7
Medication diabetes (%)	69 (98.6)	19 (95.0)
Oral hypoglycemic agents (%)	47 (67.1)	13 (65.0)
Metformin (%)	42 (60.0)	12 (60.0)
Insulin (%)	57 (81.4)	14 (70.0)
Microvascular complications (%)	47 (67.1)	14 (70.0)
Macrovascular complications (%)	21 (30.0)	10 (50.0)
Myocardial infarction (%)	14 (20.0)	9 (45.0) *
PTCA (%)	13 (18.6)	2 (10.0)
CABG (%)	8 (11.4)	8 (40.0) *
Stroke (%)	5 (7.1)	1 (5.0)
Peripheral arterial disease (%)	4 (5.7)	4 (20.0) *

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	TE result \leq 8.7 kPa (N=70)	TE result $>$ 8.7 kPa (N=20)
Liver stiffness (kPa)	5.8 [4.3-7.4]	12.2 [10.2-20.4]
IQR (kPa)	0.9 [0.5-1.3]	2.9 [2.2-3.8]
IQR/median (%)	16 [11-23]	22 [16-28]

Results are expressed as n(%), mean \pm SE or median [IQR]. * p-value <0.05 , comparison between groups. Abbreviations: BMI, Body Mass Index; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting; IQR, interquartile range.

This study is one of the first to study the effect of the Fibroscan, nevertheless limitations of the present study should be mentioned. First and foremost, we did not compare the FibroScan to the gold standard (liver biopsy) to confirm a valid measurement. Furthermore, the generalizability of the findings of the present study are limited by the relative small study size of Caucasian patients and the lack of a pre-study power calculation. On the other hand, study provides information regarding the clinical applicability of TE using the FibroScan in T2DM patients during real-life circumstances.

Nevertheless, at the moment the use of routinely performing TE as a screening instrument should not be recommended. Whether TE could be used for excluding advanced fibrosis instead of liver biopsy in T2DM should preferably be investigated in patients with an indication for liver biopsy, combining TE measurements with the liver biopsy information.

LIST OF ABBREVIATIONS

BMI	=	Body Mass Index
IQR	=	Interquartile Range
NAFLD	=	Non-Alcoholic Fatty Liver Disease
NASH	=	Non-Alcoholic SteatoHepatitis
T2DM	=	Type 2 Diabetes Mellitus
TE	=	Transient Elastography

AUTHORS' CONTRIBUTION

GWDL, NK and PHPG designed the study; PRVD and SH acquired the data used in this study; PRVD, GWDL, SH, NK and PHPG analyzed and interpreted the data; SH performed the statistical analyses; PRVD, SH and GWDL drafted the manuscript; PRVD, GWDL, SH, NK, HJGB, PHPG participated in revision of the manuscript. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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